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Dkt. No.: PP01463.002
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PATENT

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Michelle Hobson
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

POLO et al.

Serial No.: 09/546,201

Filing Date: April 10, 2000

Title: ENHANCEMENT OF THE IMMUNE
RESPONSE FOR VACCINE AND GENE
THERAPY APPLICATIONS

Examiner: S. Foley

Group Art Unit: 1648

Confirmation No.: 3605

Customer No.: 20855

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

X Reply Brief (9 pgs) with attached Claims Appendix (4 pgs)

X Return receipt postcard

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The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	17	- 20	0	x \$50.00	\$0
Independent Claims	1	- 3	0	x \$200.00	\$0
Multiple dependent claims not previously presented, add \$360.00					\$0
Total Amendment Fee					\$0
Petition for Extension of Time Fee					\$0
Small Entity Reduction (if applicable)					\$0
TOTAL FEE DUE					\$0

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: December 19, 2005

By: 
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2969
Facsimile: (510) 655-3542



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REPLY BRIEF

ROBINS & PASTERNAK LLP
1731 Embarcadero Road
Suite 230
Palo Alto, CA 94303

Attorney for Appellants

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REPLY BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

Pursuant to Section 41.37(c) (69 Fed. Reg. 49962, Aug 2004), Applicants submit the following Reply Brief in Response to the Examiner's Answer mailed on October 19, 2005. This Reply Brief is submitted within two months of the date of mailing of the Examiner's Answer, namely by December 19, 2005. Appellants respectfully request that the decision of the Examiner be reversed.

I. STATUS OF THE CLAIMS

Claims 26, 28-31 and 33-44 are currently pending as shown in the Claims Appendix and remain rejected under 35 U.S.C. § 103(a).

II. GROUNDS OF REJECTION

1. Claims 26, 28-31 and 33-44 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,015,686 (hereinafter "Dubensky"), Cella et al. (1999) *J. Exper. Med.* 189(5):821-829 (hereinafter "Cella"), U.S. Patent No. 5,736,388 (hereinafter "Chada") and WO 90/14090 (hereinafter "Gillespie").

VII. ARGUMENTS

1. A *Prima facie* Case of Obviousness Has Not been Established

All of the pending claims remain rejected as allegedly obvious over U.S. Patent No. 6,015,686 (hereinafter "Dubensky"); Cella et al. (hereinafter "Cella") and U.S. Patent No. 5,736,388 (hereinafter "Chada") and WO 90/14090 (hereinafter "Gillespie").

Appellants incorporate herein all the arguments set forth in their Appeal Brief. Rather than reiterate each argument herein, Appellants address various assertions set forth in the Examiner's Answer, in which it was again maintained that the claims are obvious over Dubensky in combination with Cella, Chada and Gillespie. In particular, the Examiner again asserted:

- Dubensky's disclosure of vectors including multiple heterologous sequences where one of the heterologous sequences is an antisense sequence is sufficient motivation to arrive at vectors encoding an antigen and a sequence that forms double-stranded RNA via self-complementation. (Examiner's Answer, pages 5 and 12).

- Gillespie's disclosure of dsRNA RNA that forms via self-complementation and induces interferon provides the motivation to substitute self-complementing RNA for Dubensky's antisense RNA. (Examiner's Answer, page 12).
- Chada's disclosure of eukaryotic layered vector initiation systems including two promoters to increase expression of each heterologous gene provides the motivation to modify Dubensky's vectors to include two promoters. (Examiner's Answer, page 7).

It is respectfully submitted that of these assertions are based on improper picking and choosing of individual elements and improper hindsight reconstruction and, accordingly, cannot support a *prima facie* case of obviousness.

In particular, the alleged motivation to combine the references (namely, the fact that dsRNA was known to induce interferon production) does not consider whether the cited references suggest the *desirability* of the claimed invention, not merely whether the individual elements are all set forth. *See, e.g., Amgen, Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious;" *In re Laskowski*, 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification"; and *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004) stating that "[t]he question is whether there is something in the prior art as a whole to suggest the desirability."

The Examiner acknowledges that Dubensky and Chada do **not** teach or suggest dsRNA formed via self-complementation. *See*, Examiner's Answer, pages 5 and 9. Although Gillespie teaches dsRNA formed via self-complementation *in vitro*, none of the cited references teach or suggest the *desirability* of replacing Dubensky's or Chada's antisense sequences (which bind to native transcripts) with dsRNA that forms via self-complementation.

At issue is whether induction of interferon by any dsRNA provides one of ordinary skill with motivation to combine Dubensky/Chada and Gillespie as set forth in the rejection. In this regard, the Examiner alleges that Dubensky's indication that sufficient quantities of antisense RNA must be present actually provides further motivation to use Gillespie's self-complementing sequences in Dubensky's vectors, based on the notion that self-complementing dsRNA and antisense are interchangeable because of the known ability of dsRNA to induce interferon production. *See*, Examiner's Answer, page 13.

However, as previously noted, the obviousness rejection (or motivation to combine Dubensky and/or Chada with Gillespie or Cella) **cannot** be predicated on the notion that dsRNA was known to induce interferon production. Dubensky and/or Chada do not teach that dsRNA molecule will induce interferon production. Rather, these references teach that inducing interferon production **requires** the use of **specific** antisense molecules (Dubensky, col. 23, lines 1-8 and Chada, col. 23, lines 56-62, emphasis added):

Briefly, in addition to binding RNA and thereby preventing translation of a specific mRNA, high levels of specific antisense sequences are believed to induce the increased expression of interferons (including gamma-interferon) due to the formation of large quantities of double-stranded RNA.

Within other embodiments of the invention, the cytotoxic gene may include an antisense molecule which inhibits, for example, tumor cell growth, viral replication, or a genetic disease by preventing the cellular synthesis of critical proteins needed for cell growth. Antisense RNA may be utilized as a cytotoxic gene in order to induce a potent Class I restricted response, as in high levels of specific antisense sequences may be utilized to induce the increased expression of interferons (including γ -interferon), due to the formation of large quantities of double-stranded RNA, which, in turn, boosts the expression of MHC Class I antigens.

Given Dubensky and Chada's teachings regarding induction of interferon by specific antisense sequence, it is respectfully submitted that induction of interferon production by dsRNA would not have provided one of ordinary skill in the art sufficient motivation to substitute

antisense-encoding sequences with dsRNA formed via self-complementation *in vivo* after expression. Neither Dubensky nor Chada suggests such a substitution. Indeed, Dubensky and/or Chada cannot suggest anything regarding bifunctional constructs as claimed since these references do not teach anything about how dsRNA can be formed by self-complementation. Including antigen encoding sequences and antisense encoding sequences in the same construct does not teach or suggest anything about bifunctional cassettes including dsRNA formed via self-complementation, as claimed.

For their parts, Gillespie and Cella do not provide the motivation missing from Dubensky and Chada, as both are silent as to whether specific antisense molecules regarding interferon induction. Gillespie and Cella are directed instead to short dsRNA sequences formed *in vitro* and do not suggest the interchangeability of such dsRNA with specific antisense sequences, let alone the desirability of making such a substitution.

Furthermore, contrary to the Examiner's assertions, neither Gillespie nor Cella suggest the desirability of *in vivo* expression of the dsRNA. Rather, both references teach that the RNA is pre-annealed to form dsRNA before administration to cells. *See, e.g.*, Section 3 of Gillespie, including page 7, lines 19-21 stating that antitumor properties can be measured by "injecting dsRNA into nude mice...;" Section 4 on page 8 stating that "suitable test animals ... can be injected periodically with various quantities of dsRNA...;" claims 9-16, all of which are drawn to methods comprising "administering ... a therapeutically effective amount of the short dsRNAs of defined structure..."

Thus, the fact remains that antisense and self-complementing dsRNA are **not** interchangeable and the references teach away from assuming such interchangeability. Dubensky and Chada, which do not teach or suggest dsRNA formed via self-complementation, disclose that antisense sequences may induce interferon production, if the antisense sequences are specific and present at high enough levels. However, this doesn't provide the requisite suggestion that dsRNA formed via self-complementation could be used instead of antisense. Gillespie and Cella are silent as to specific antisense molecules. Therefore, one of ordinary skill

in the art would read Dubensky and Chada as teaching away from using self-complementing dsRNA instead of antisense because self-complementing dsRNA is not specific and the quantities needed are unknown.

Simply identifying the various elements of a claim in separate documents is **not** enough to support a *prima facie* case of obviousness. Absent the suggestion that an expression cassette that includes antigen-encoding sequences and sequences that form dsRNA via self-complementation would be desirable, the rejection can only be based on improper hindsight reconstruction.


Thus, the cited references do not teach or suggest the expression cassettes as claimed. Nor do the references provide the requisite motivation to combine their individual elements in the manner set forth in the claims. The alleged motivation to combine (inducing interferon production) is not present because the references and art as a whole do not teach that dsRNA formed by pairing of specific antisense sequences with native transcripts (Dubensky and Chada) is interchangeable with dsRNA formed prior to administration. There is no suggestion that the claimed expression cassettes would be desirable. As such, a rejection can only be based on improper hindsight reconstruction. Without the benefit of Appellants' disclosure, there is no motivation or suggestion regarding the desirability of substituting Gillespie's or Cella's preformed dsRNA for Dubensky's specific antisense. Accordingly, a *prima facie* case of obviousness has not been (and indeed cannot be) presented by the Office. Withdrawal of the rejection is in order.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are non-obvious over the cited references. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: December 19, 2005

By: 
Dahna S. Pasternak
Registration No. 41,411
Attorney for Appellants

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440

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CLAIMS APPENDIX

CLAIMS INVOLVED IN THE APPEAL

1 to 25. (canceled).

26. (previously presented): An expression cassette comprising
a promoter operably linked to a nucleic acid molecule which, when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences within the RNA, wherein the double stranded RNA induces the production of interferon, and
an RNA polymerase II promoter operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent.

27. (canceled).

28. (previously presented): The expression cassette according to claim 26 wherein said antigen is a viral antigen.

29. (original): The expression cassette according to claim 28 wherein said viral antigen is selected from the group consisting of HIV, HSV, HBV, HCV, HPV, and FIV.

30. (previously presented): The expression cassette according to claim 26 wherein said pathogenic agent is a bacteria, parasite or fungus.

31. (previously presented): The expression cassette according to claim 26 wherein said pathogenic agent is a tumor.

32. (canceled).

33. (original): The expression cassette according to claim 26 wherein said pol II promoter is selected from the group consisting of CMV, SV40, MoMLV LTR and RSV LTR.

34. (previously presented): A gene delivery vector, comprising an expression cassette according to claim 26.

35. (original): The gene delivery vector according to claim 34 where said vector is a plasmid.

36. (original): The gene delivery vector according to claim 34 where said vector is a recombinant retrovirus.

37. (original): The gene delivery vector according to claim 34 where said vector is a recombinant herpesvirus.

38. (original): The gene delivery vector according to claim 34 where said vector is a recombinant poxvirus.

39. (original): The gene delivery vector according to claim 34 where said vector is a recombinant adenovirus.

40. (original): The gene delivery vector according to claim 34 where said vector is a recombinant parvovirus.

41. (original): The gene delivery vector according to claim 34 where said vector is a recombinant alphavirus.

42. (original): The gene delivery vector according to claim 34 where said vector is a recombinant polyoma virus.

43. (previously presented): The gene delivery vector according to claim 34 where said vector is a eukaryotic layered vector initiation system vector.

44. (previously presented): A cell which contains a gene delivery vector according to claim 34.

45. (canceled).